IMMORTALIZATION AND TUMORIGENESIS

ONCOL 520. Feb. 7, 2012
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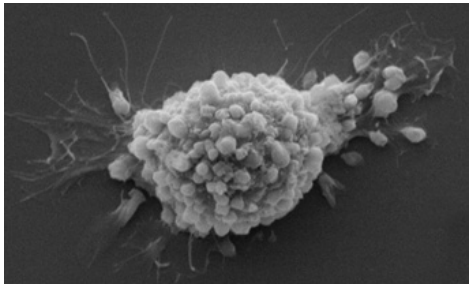
The Biology of Cancer (Weinberg)
Chapter 10



LECTURE OUTLINE

- What is senescence?
- What signals induce senescence?
- Role of telomeres in limiting replication.
- End Replication Problem
- Telomerase

PROLIFERATIVE CAPACITY OF CELLS IN CULTURE

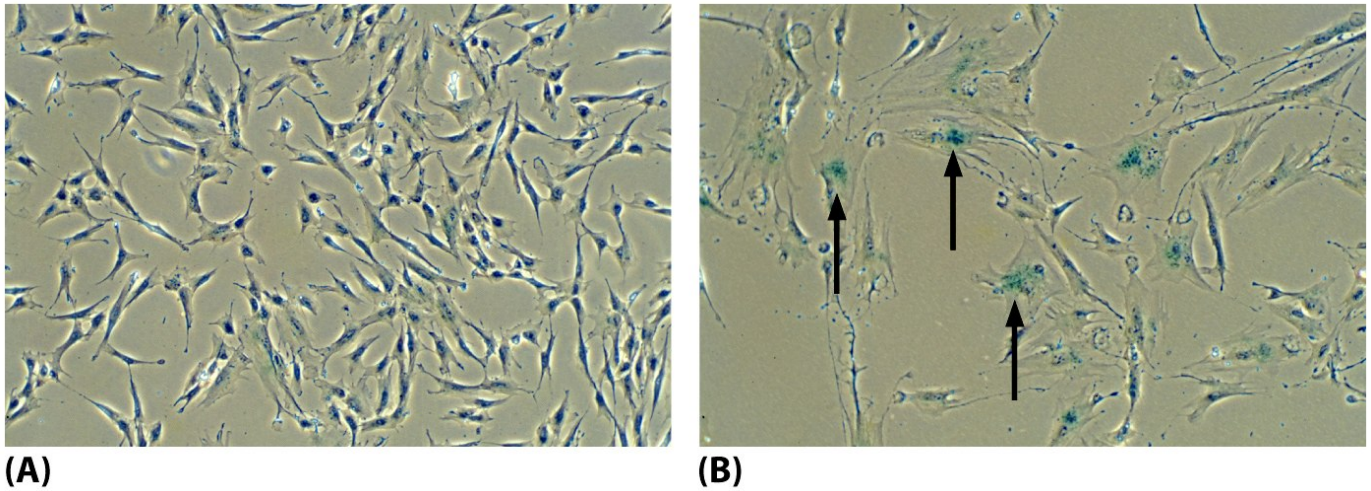


Figure 10.3 *The Biology of Cancer* (© Garland Science 2007)

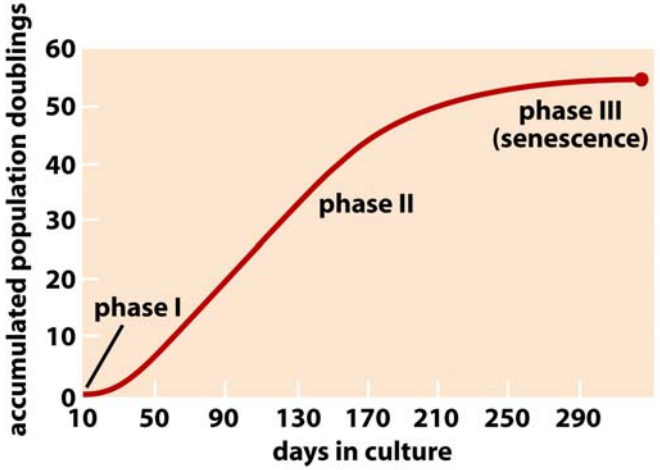


Figure 10.2 *The Biology of Cancer* (© Garland Science 2007)

SENESCENCE

- In 1965, Leonard Hayflick reported cells in culture stop proliferating after a fixed number of divisions.
  - "The finite lifetime of diploid cell strains in vitro may be an expression of aging or senescence at the cellular level." Haflick limit
- Cells remain metabolically active.
- Unable to re-enter the cell cycle.
- Morphology
  - Spread out, flattened with a large cytoplasm
- Cells prepared from embryos undergo more population doublings than cells from adult tissue.
- Cells prepared from embryonic stem cells show unlimited replicative potential.

SV40 LARGE T ANTIGEN INHIBITS SENESCENCE

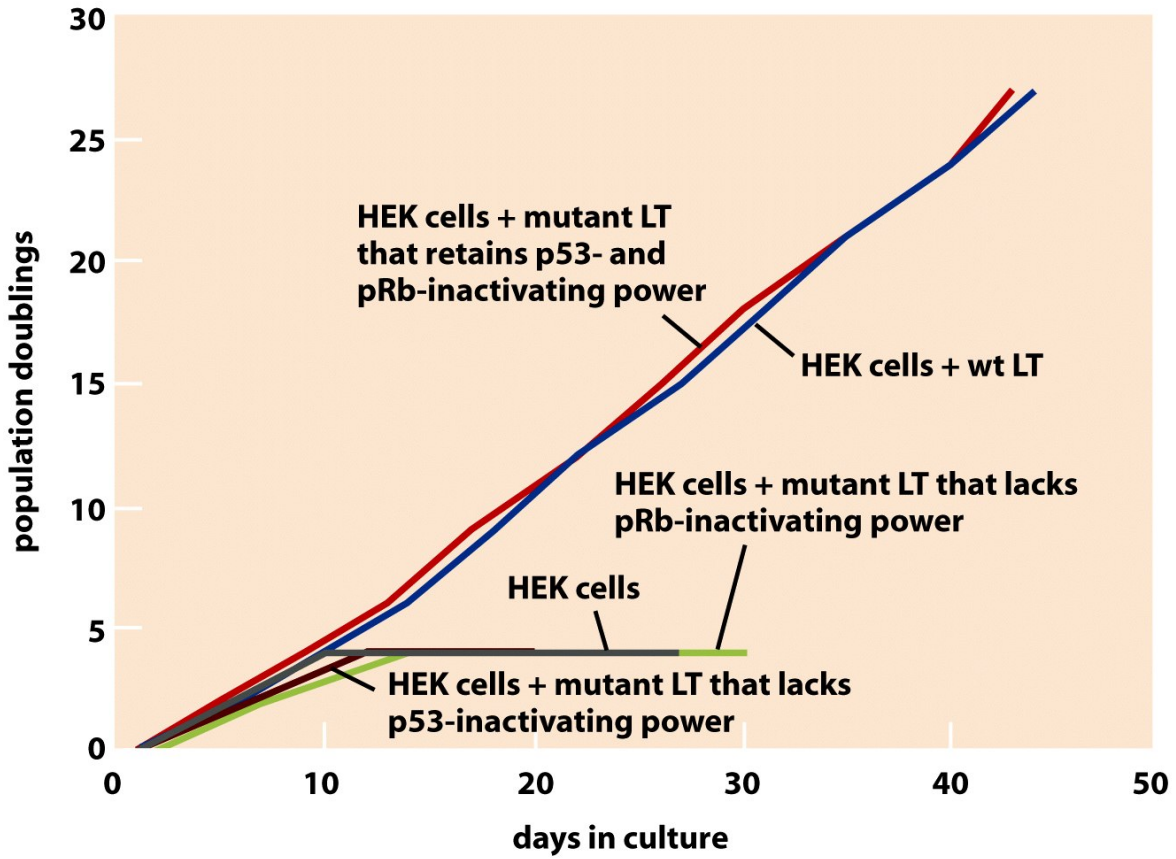


Figure 10.8 *The Biology of Cancer* (© Garland Science 2007)

SV40 LARGE T ANTIGEN INHIBITS SENESCENCE

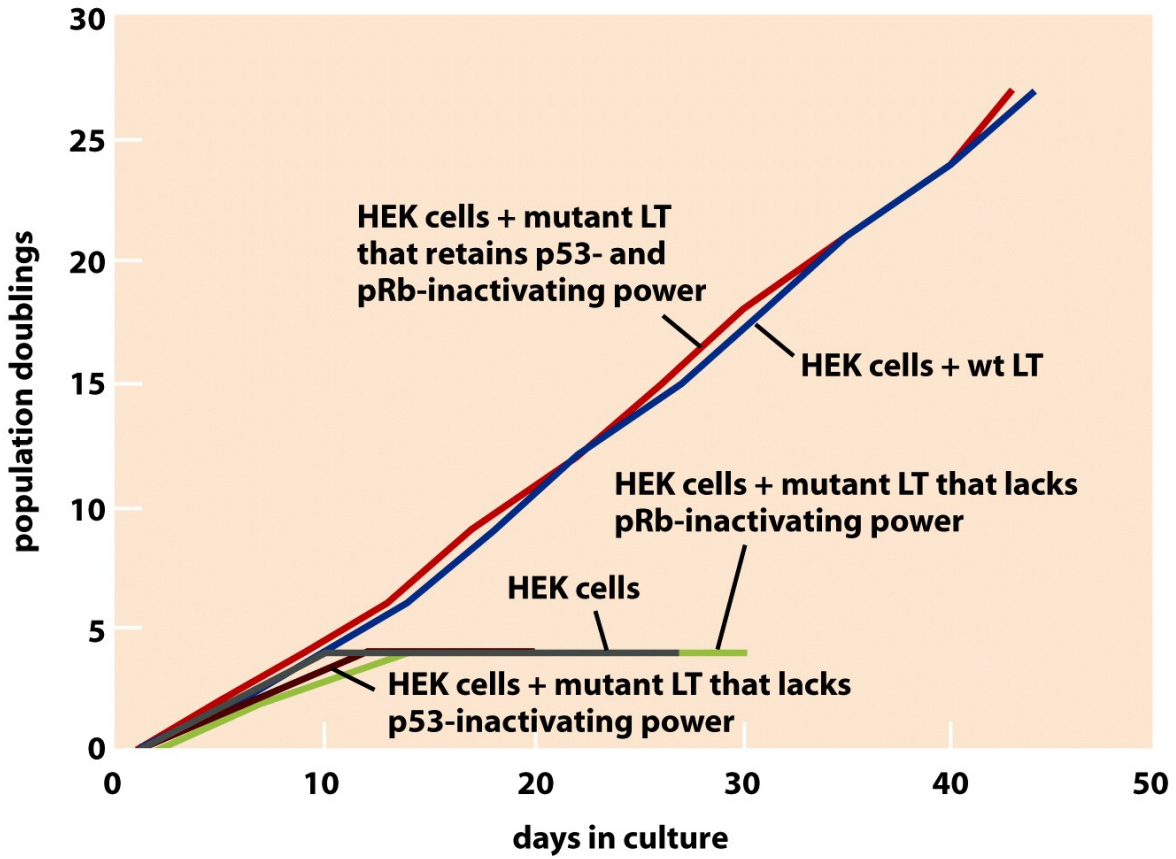


Figure 10.8 *The Biology of Cancer* (© Garland Science 2007)

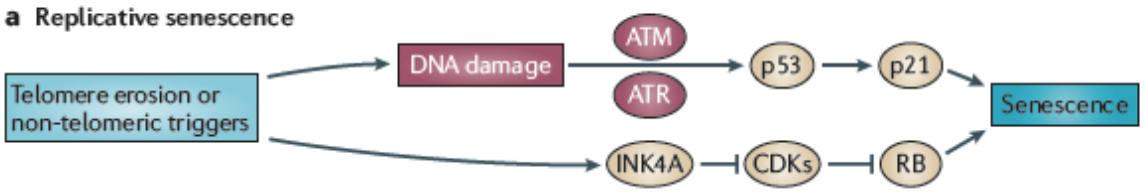
This escape from senescence lasts for a limited number of proliferations.

Ultimately, cells undergo crisis, chromosomal instability and death.

LECTURE OUTLINE

- What is senescence?
- What signals induce senescence?

SENESCENCE



Nardella et al. 2011. Nature Reviews Cancer 11: 503.

TELOMERES

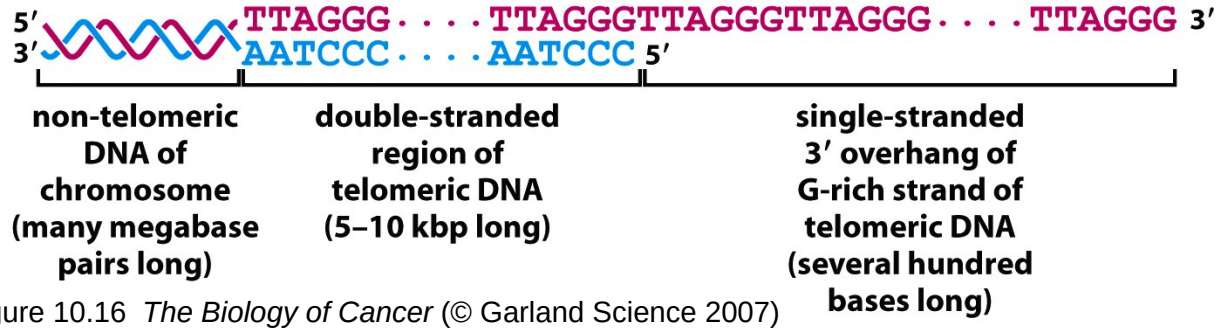


Figure 10.16 *The Biology of Cancer* (© Garland Science 2007)

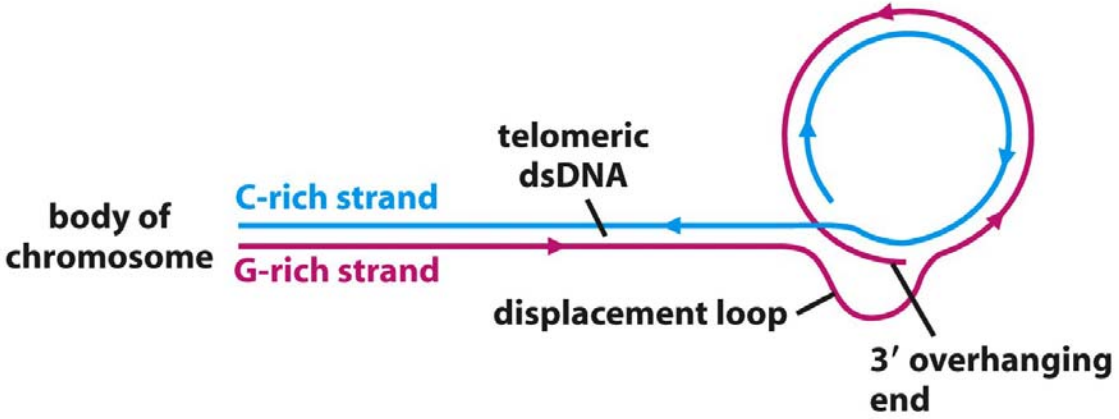


Figure 10.17b *The Biology of Cancer* (© Garland Science 2007)

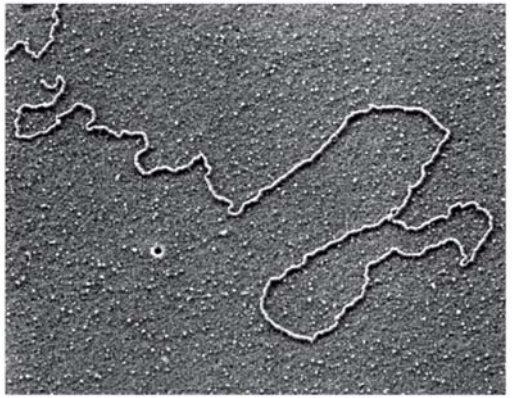


Figure 10.17a *The Biology of Cancer* (© Garland Science 2007)

END REPLICATION PROBLEM

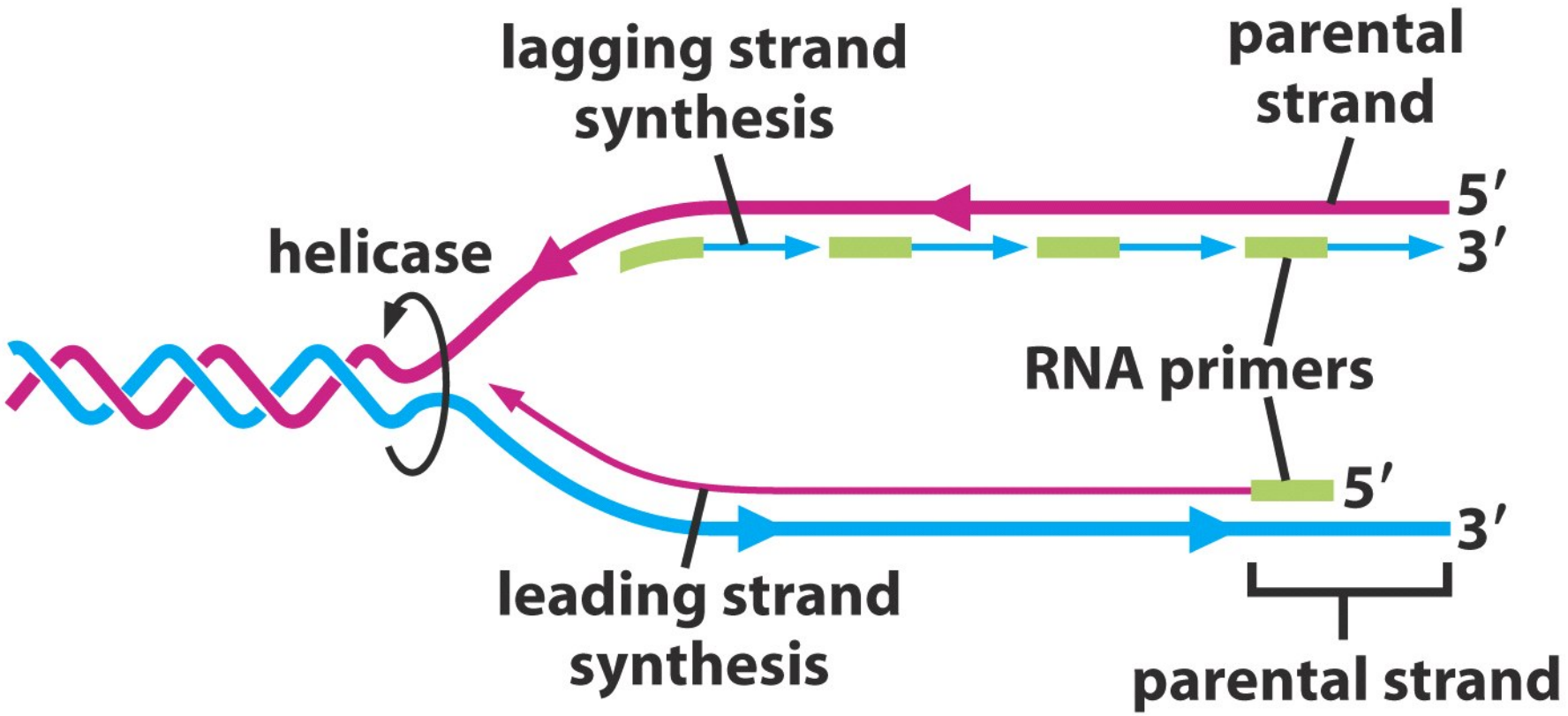


Figure 10.20 *The Biology of Cancer* (© Garland Science 2007)

END REPLICATION PROBLEM

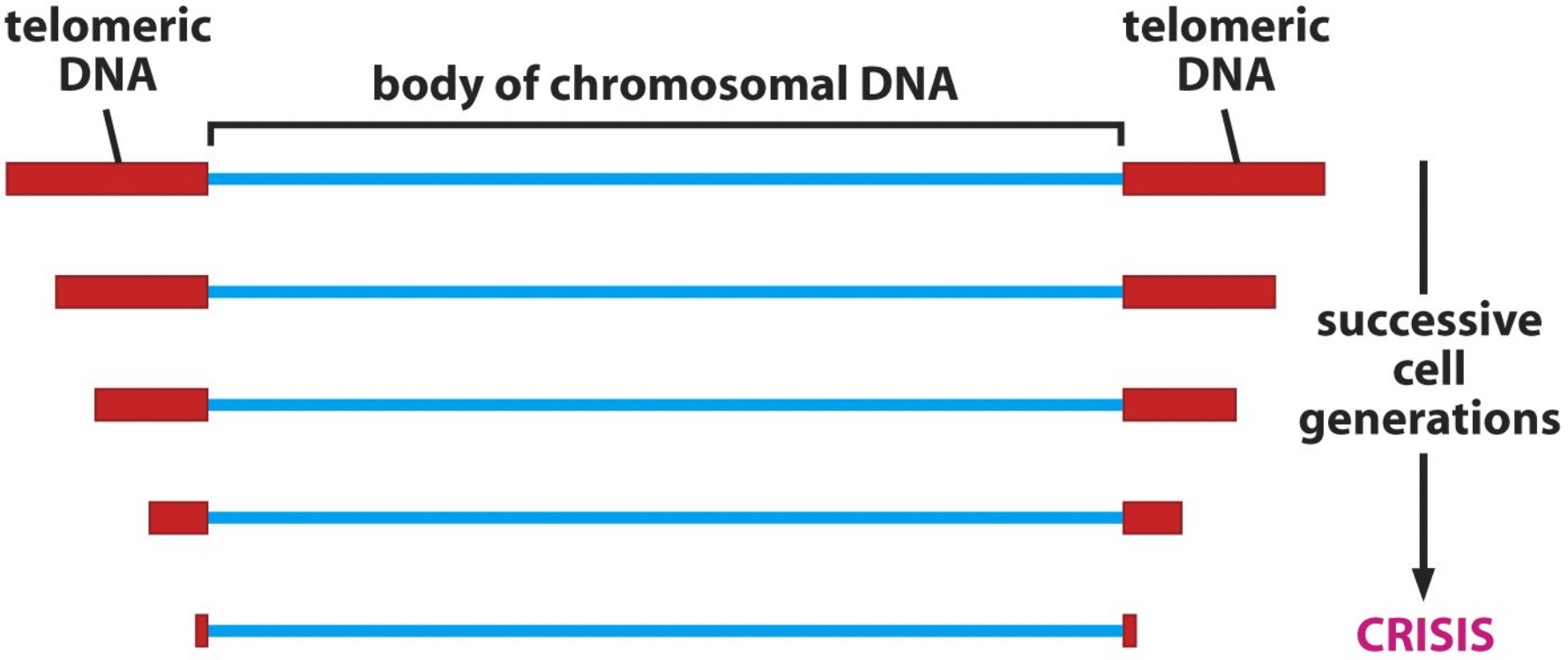


Figure 10.13b *The Biology of Cancer* (© Garland Science 2007)

END REPLICATION PROBLEM

- Induces crisis—cell death.
- Is a block to cellular immortality.
- Can cause chromosomal instability.
- Is not a problem in stem cells, cancer cells.
- Why?

CHROMOSOMAL INSTABILITY IF NORMAL QUALITY CONTROL PATHWAY IS ABERRANT. BREAKAGE-FUSION-BRIDGE CYCLES

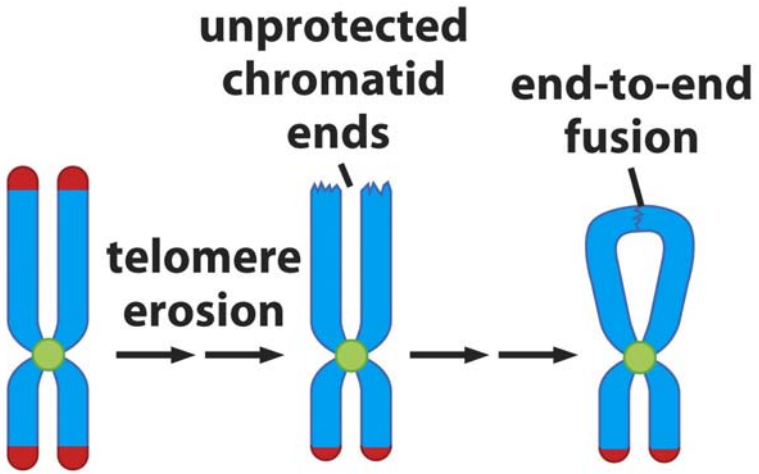


Figure 10.14a *The Biology of Cancer* (© Garland Science 2007)

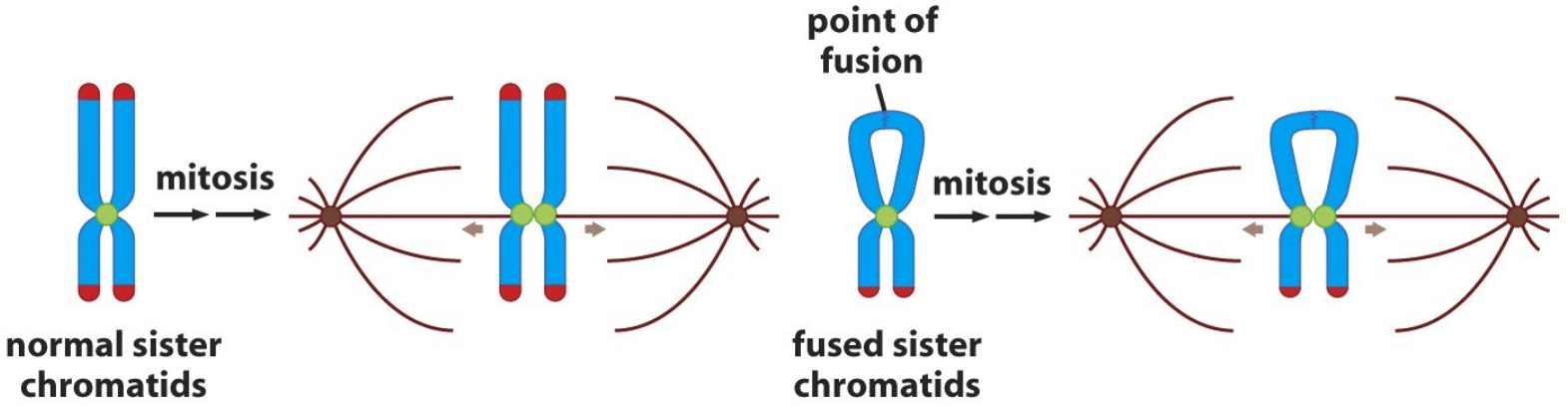


Figure 10.14b *The Biology of Cancer* (© Garland Science 2007)

BREAKAGE-FUSION-BRIDGE CYCLES

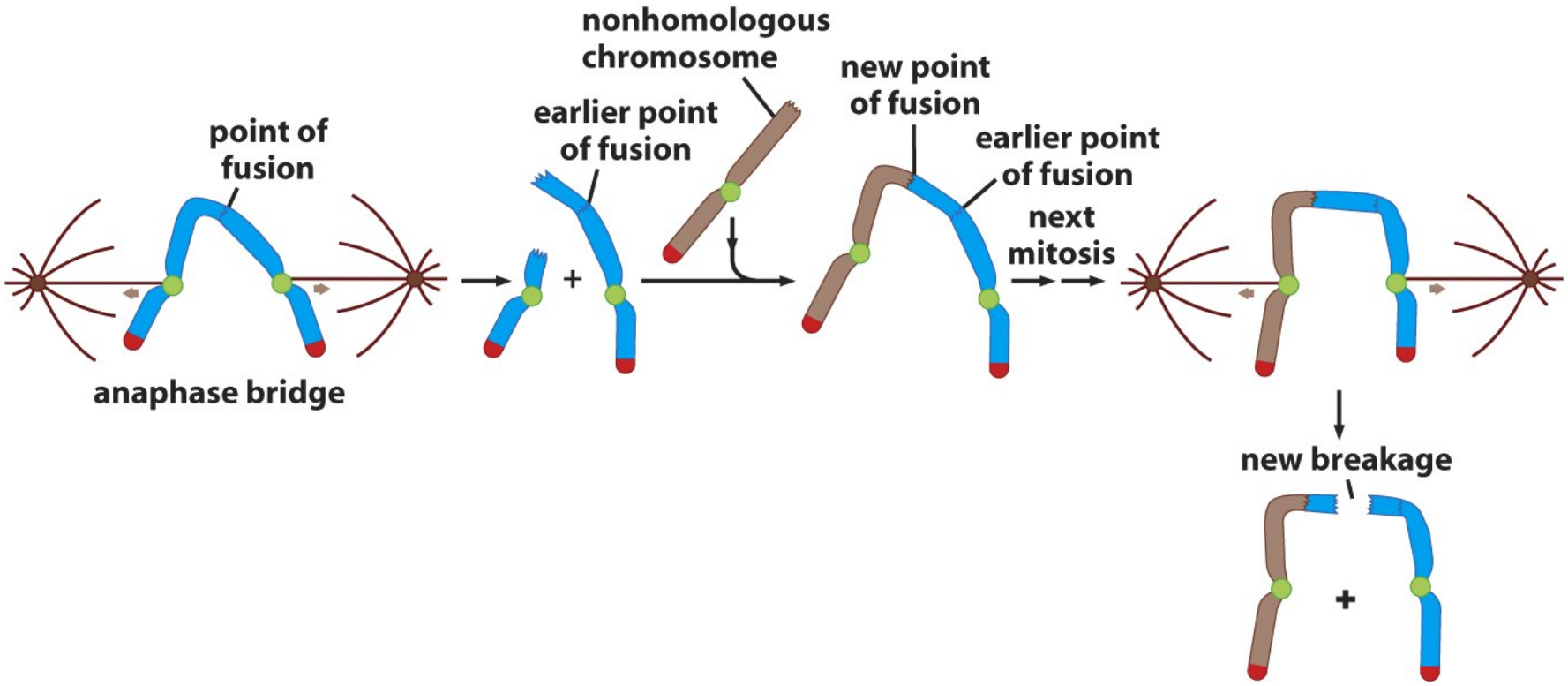


Figure 10.14c *The Biology of Cancer* (© Garland Science 2007)

END REPLICATION PROBLEM

- Induces crisis—cell death.
- Is a block to cellular immortality.
- Can cause chromosomal instability.
- Is not a problem in stem cells, cancer cells.
- Why?

TELOMERASE

- Enzymatic complex that elongates telomeres.
- Present in stem cells, 85-90% tumors, low levels in most normal cells.
- Contains DNA polymerase (reverse transcriptase)--hTERT.
- Contains RNA template—hTR.

TELOMERASE

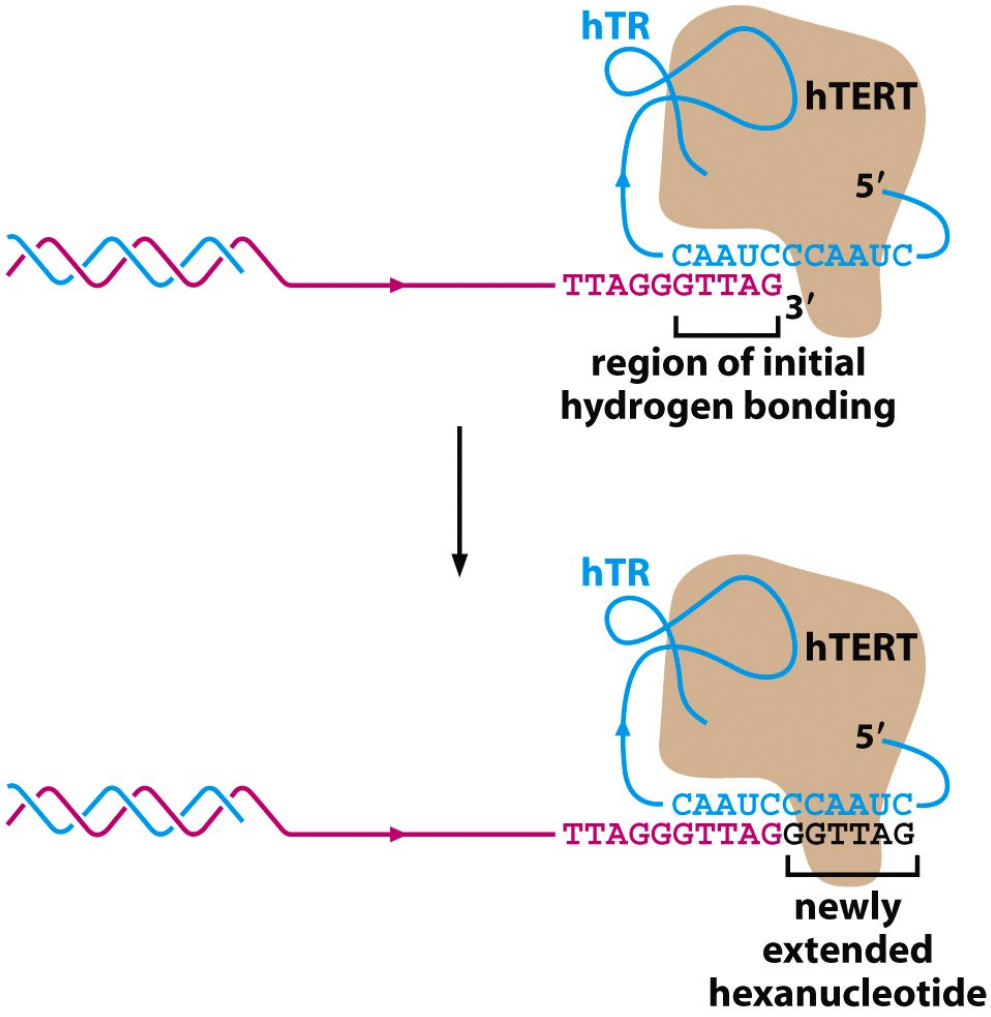


Figure 10.23a *The Biology of Cancer* (© Garland Science 2007)

TELOMERASE PREVENTS CRISIS IN VITRO

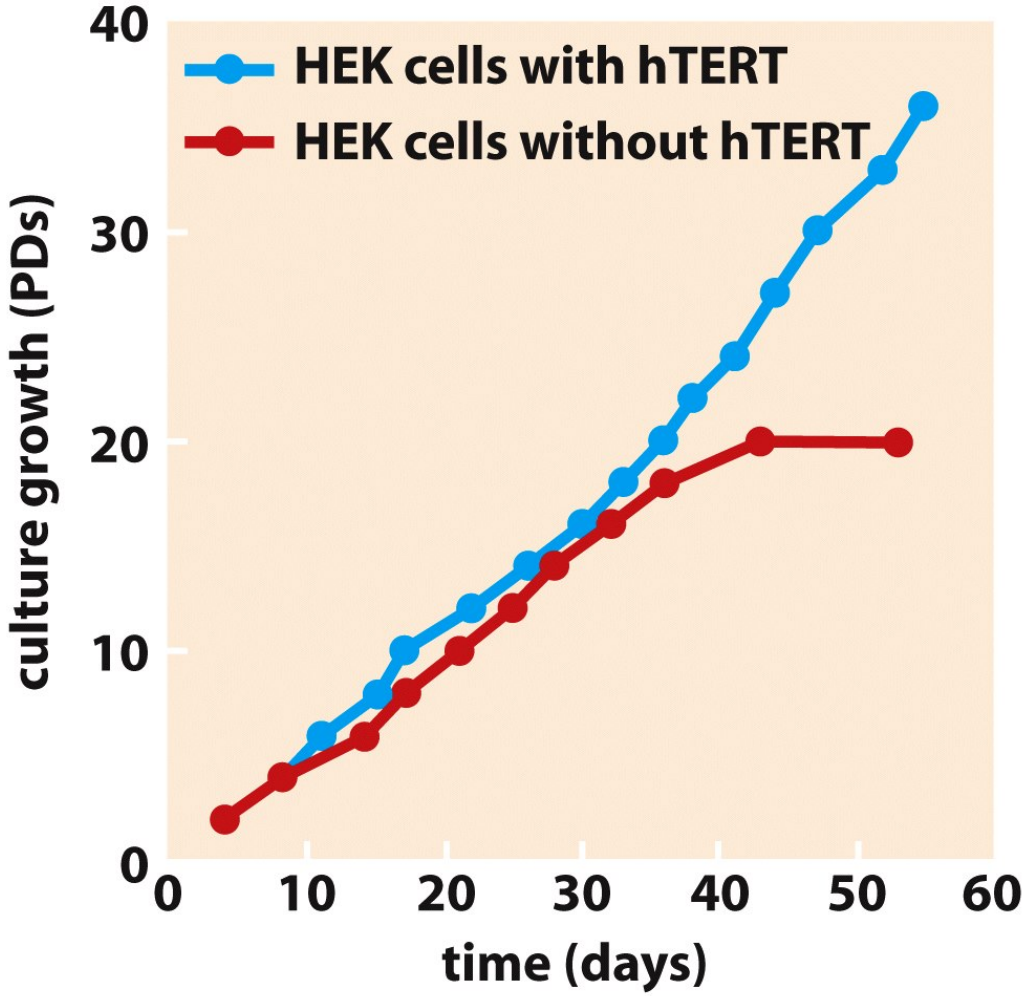


Figure 10.25b *The Biology of Cancer* (© Garland Science 2007)

TELOMERASE IS ASSOCIATED WITH CANCER PROGRESSION

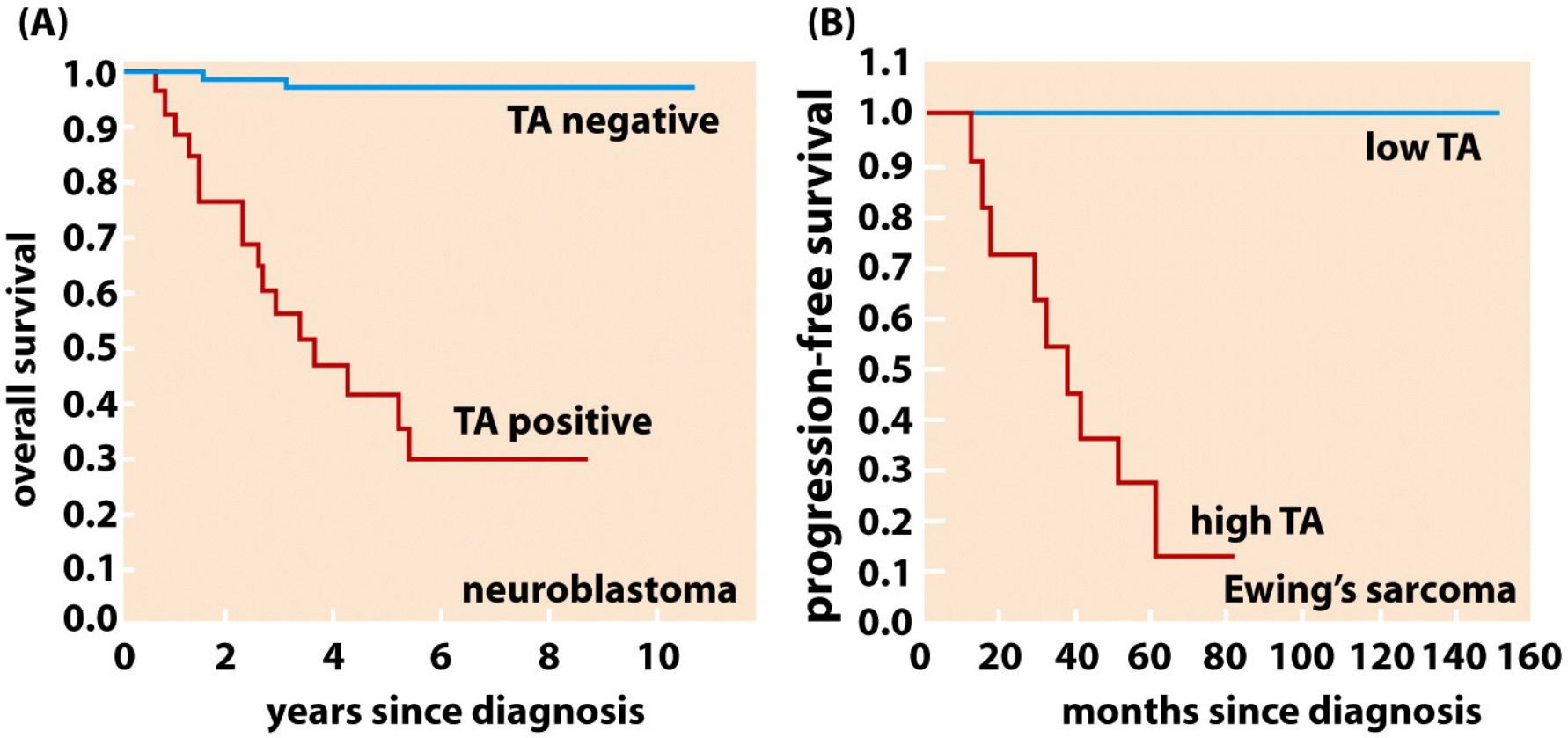
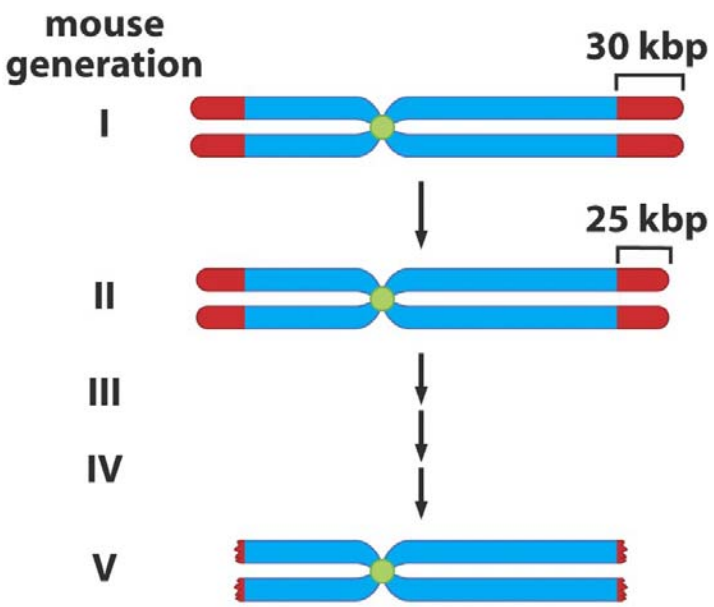
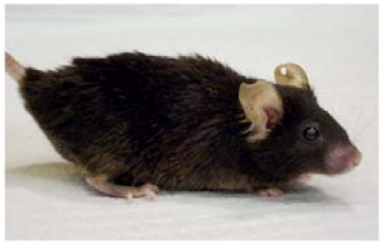


Figure 10.28 *The Biology of Cancer* (© Garland Science 2007)

TELOMERASE STUDIES IN MICE





-mTR$^{-/-}$ mice are phenotypically normal for the first 3 generations.
-later generations, telomeres have eroded to an extent, that tissues cannot renew themselves.
-mice show signs of premature aging.

Figure 10.31 *The Biology of Cancer* (© Garland Science 2007)

Why did it take 3 generations before mice showed signs of premature aging?
-mice live only 1% of human lifespan.
-humans have 10^{16} mitoses in a lifetime, whereas mice have 10^{11}.

CARCINOMA FORMATION/ANEUPLOIDY OF HUMAN CARCINOMA

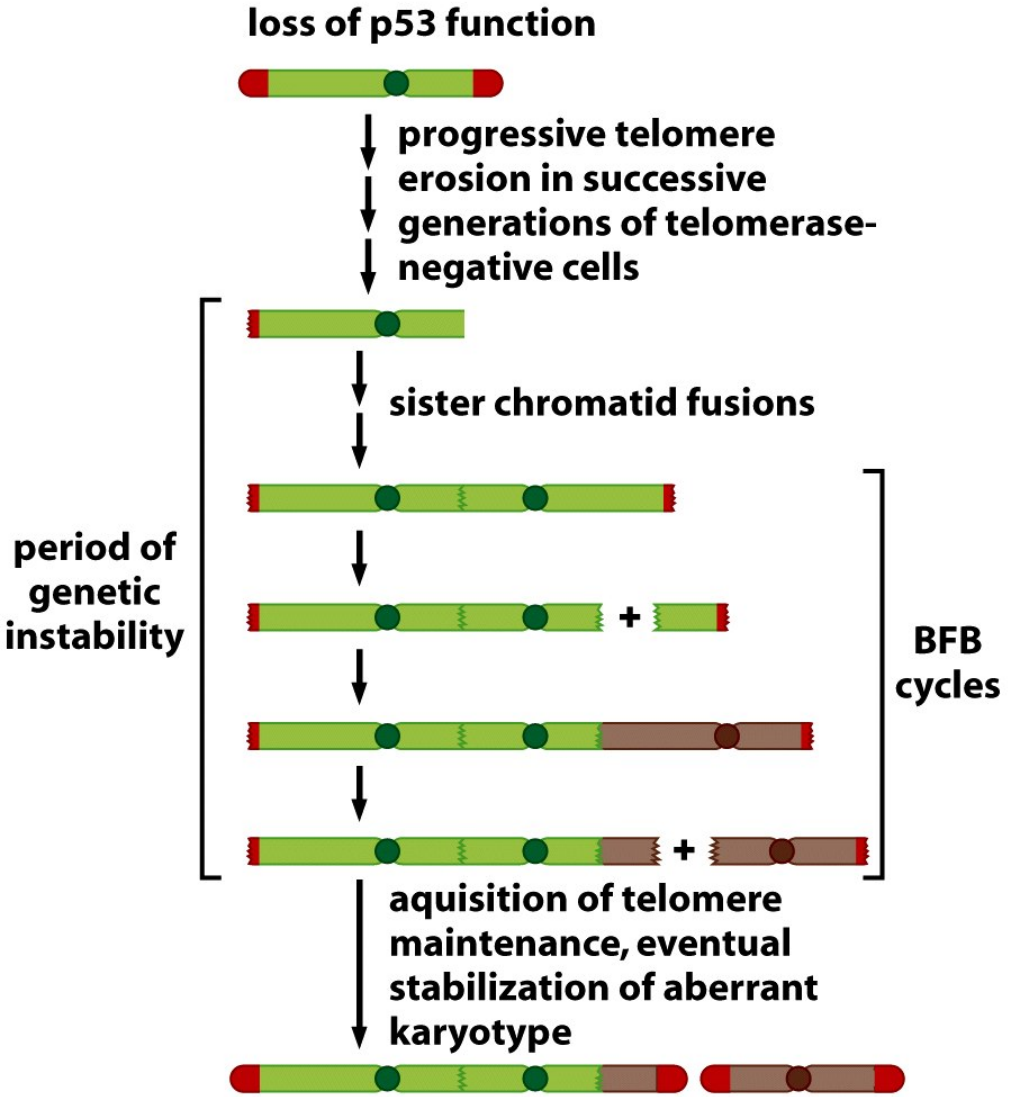
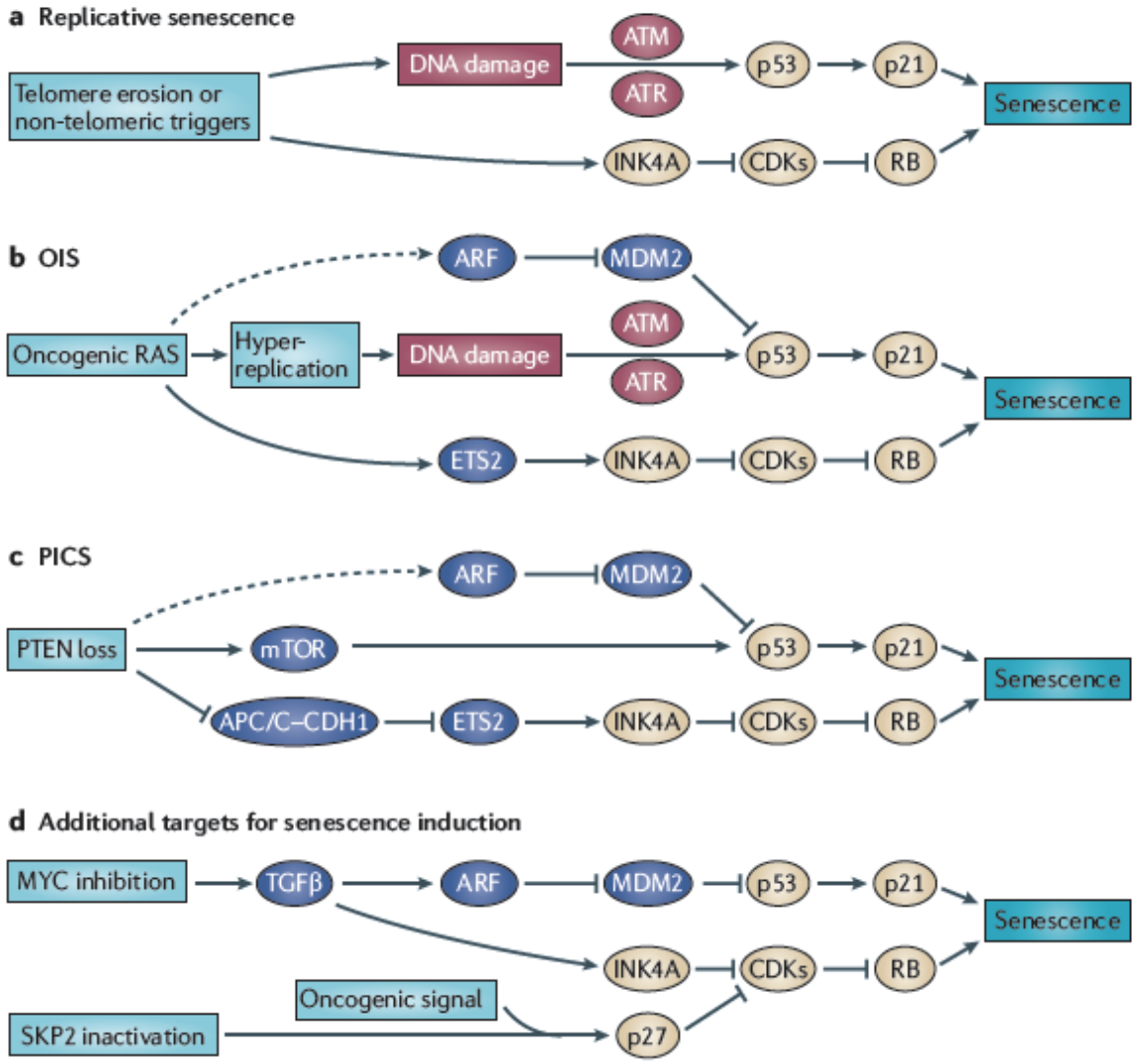


Figure 10.35 *The Biology of Cancer* (© Garland Science 2007)

DIFFERENTIAL SENESCENCE RESPONSES



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